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Gene Section
Review

PDSS2 (prenyl (decaprenyl) diphosphate synthase, subunit 2)

Ping Chen, Qi Chen

Department of genetics and Molecular Biology, Xi'an Jiaotong University School of Medicine, Xi'an 710061, China (PC), Department of Pharmacology, Toxicology, and Therapeutics, University of Kansas Medical Center, Kansas City, KS, 66160, USA (QC)

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Abstract

Review on PDSS2, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: C6orf210, COQ10D3, DLP1, bA59I9.3, hDLP1

HGNC (Hugo): PDSS2

Location: 6q21

Local order

According to NCBI Map Viewer, several genes flank PDSS2 in the order from centromere to telomere direction on chromosome: 6; NC_000006.11:

- C6orf203, chromosome 6 open reading frame 203, location: 6q21;
- BEND3, BEN domain containing 3, location: 6q21;
- RPS24P12, ribosomal protein S24 pseudogene 12, location: 6q21;
- PDSS2, 6q21;
- SOBP, sineoculis binding protein homolog (Drosophila), location: 6q21.

DNA/RNA

Description

PDSS2 gene has 307.02 kb of genomic DNA on the reverse strand, containing 8 exons.

Transcription

The full transcript is a 3568 bp mRNA with 1200 bp open reading frame. This gene has 4 transcripts (splice variants, PDSS2-001 to 004). All transcripts are protein coding. The length of the 4 splice variants are 3540 bp (399 aa), 1338 bp (297 aa), 1236 bp (240 aa) and 241 bp (80 aa) respectively.

Protein

Human decaprenyl diphosphate synthase is a hetero-tetramer composed of DPS1 (PDSS1; NM_014317) and DLP1 (PDSS2) subunits that produces the ubiquinone coenzyme Q10.

The isoprenoid chain of ubiquinone (coenzyme Q) varies in length between species and is determined by trans-polyprenyl diphosphate synthase.

Other names: decaprenyl pyrophosphate synthetase subunit 2; prenyl diphosphate synthase, subunit 2; subunit 2 of decaprenyl diphosphate synthase.

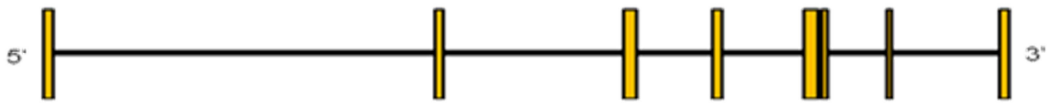

Diagram of the PDSS2 gene (isoform1/Dlp1). Exons are represented by open boxes (in yellow). Exons 1 to 8 are from the 5' to 3' direction.

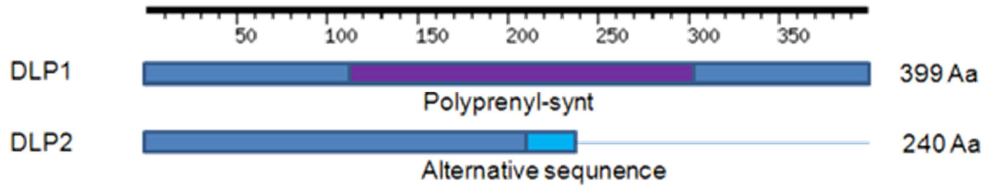

Diagram of 2 isoforms of PDSS2 protein (DLP1and DLP2).

Description

The complete translation product is a 44 kDa protein containing 399 amino acids. It is the non-catalyzing subunit of prenyl diphosphate synthase, the first enzyme in CoQ10 biosynthesis. However it is essential for the activity of the enzyme. Its mutations could cause CoQ10 deficiency and contributes to nephritic and metabolic diseases and neuromuscular defects.

It is also a candidate tumor suppressor protein, and was found down-regulated in melanoma, gastric cancer and non-small-cell lung cancers.

A mutated protein was identified by Saiki et al. (2005) that contains the 7 conserved domains typically found in all trans-prenyl diphosphate synthases, but it lacks DDxxD motifs which could be involved in the catalytic mechanism and/or the binding of the substrates.

Expression

According to AceView, this gene is expressed at high level, 2.1 times the average genes, observed from 226 cDNA clones.

Northern blot analysis shows PDSS2 expresses two transcripts: 3.5 and 1.2 kb. The 3.5-kb transcript was expressed strongly in heart, prostate, and testis; moderately in brain, kidney, liver, lung, spleen, duodenum, esophagus, pancreas, thymus, and thyroid; and weakly in colon, muscle, small intestine, salivary gland, and uterus, and was absent in stomach, peripheral blood lymphocyte, and urinary bladder. Expression of the 1.2-kb transcript was detected in heart, kidney, liver, pancreas, prostate, testis, thymus, and thyroid.

Localisation

Cytoplasm, organelle, mitochondria.

Function

It is the 2nd subunit of decaprenyl diphosphate synthase, which catalyzes the first and critical step in coenzyme Q biosynthesis: the formation of all trans-polyprenyl pyrophosphates from isopentyl diphosphate in the assembly of polyisoprenoid side chains. The step is critical in coenzyme Q biosynthesis. It is not the catalytic subunit but is essential for the catalytic activity.

Related super-pathways: Metabolic pathways, apoptosis, geranyldiphosphate biosynthesis, trans-octaprenyl transferase activity and protein heterodimerization activity.

Protein interaction: PDSS2 protein can interact with apoptotic protease-activating factor 1 (APAF1, DIP27624N), which mediates the cytochrome c-dependent autocatalytic activation of pro-caspase-9 (Apaf-3), leading to the ATP required activation of caspase-3 and apoptosis. Result from in silicon pathway analysis showed that PDSS2 protein could interact with hepatocyte nuclear factor 4 alpha (HNF4a), a nuclear transcription factor which regulates the expression of many genes involved in cell growth and proliferation.

Homology

PDSS2 gene is conserved in human, Rhesus monkey, dog, cow, mouse, rat, chicken, zebrafish, fruit fly, and mosquito.

Mutations

Note

PDSS2, GLN322TER [dbSNP:rs118203955]

PDSS2, SER382LEU [dbSNP:rs118203956]

Disease: Primary coenzyme Q10 deficiency-3 (COQ10D3; OMIM614652).

Two compound heterozygous mutations in the PDSS2 gene were identified by López et al. (2006) in an infant with fatal encephalomyopathy and nephrotic syndrome due to coenzyme Q10 deficiency-3 (COQ10D3; 614652): 2 mutations in the PDSS2 gene: a 964C-T transition resulting in a gln322-to-ter (Q322X,610564.0001) substitution inherited from the unaffected father; and a 1145C-T transition resulting in a ser382-to-leu (S382L; 610564.0002) substitution in the seventh conserved domain inherited from the unaffected mother (López et al., 2006).

In fibroblasts derived from the patient reported by López et al. (2006). CoQ10 levels were decreased to 22.4% of normal, and the cells showed reduced ATP levels (50% of controls), but no increase in reactive oxygen species, signs of oxidative stress, increased antioxidant defense markers,or oxidative stress-induced cell death (Quinzii et al., 2008; Quinzii et al., 2010). This suggested that the pathology caused by these PDSS2 mutations was related to the marked bioenergetic defect, but not to oxidative stress.

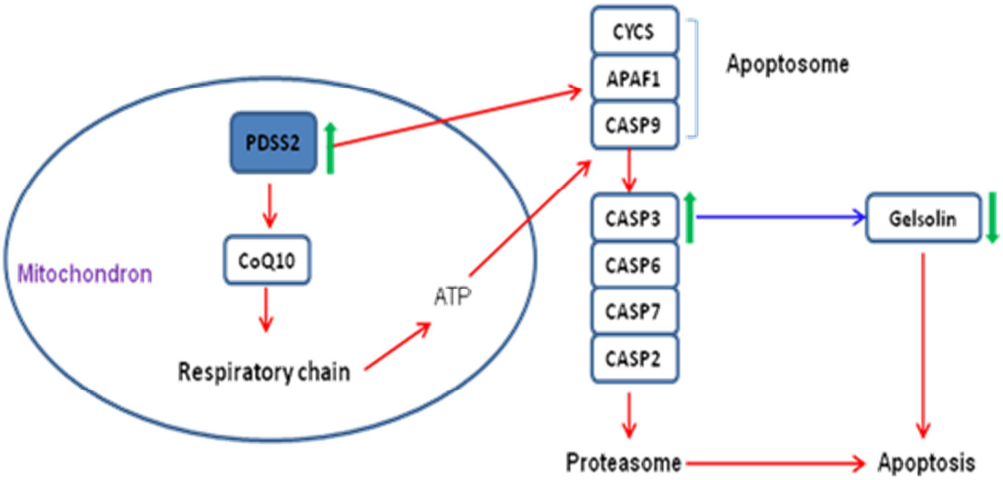

Diagram of PDSS2 possible pathway involved in produce lung cancer cells death through apoptosis.

The very low mitochondrial respiratory activity may even confer some resistance to stress-induced apoptosis.

PDSS2 polymorphisms

Disease: Leigh syndrome with nephropathy

A pair of proxy SNPs of PDSS2 was significantly associated with podocyte diseases, and patients homozygous for one PDSS2 haplotype had a strongly increased risk for podocyte disease. A deficiency of coenzyme Q10 is manifested in lymphoblastoid cell lines derived from focal segmental glomerulosclerosis patients (Gasser et al., 2013).

Implicated in

Gastric cancer

Note

PDSS2 may be a potent gastric cancer growth suppressor in vitro acting through apoptosis pathways. By transfecting PDSS2 to gastric cancer cell line SGC7901, Chen et al. found that expression of PDSS2 can induce apoptosis in human gastric cancer SGC7901 cells, block cell at G0/G1 stage, and inhibit cell proliferation.

Expression of PDSS2 is downregulated in human gastric cancer (84.6%, 33/39), and the degree of expression degraded with the increase of malignant degree of tumor. In poorly differentiated gastric cancer, the negative or low expression of PDSS2 was 35% (7/20) or 55% (11/20) and in moderately differentiated gastric cancer, it was 10.5% (2/19) or 68.4% (13/19), respectively (Chen et al., 2009).

Melanoma

Note

Down-regulation of PDSS2 was observed in 59 of 87 (67.8%) primary melanomas, which was significantly higher than that in benign nevi (7 of 66, 10.6%). An overexpression of the PDSS2 in UACC-903 cells could inhibit tumor cell growth, decrease the colony-forming ability in soft agar, and totally abrogate the tumorigenicity of UACC-903 in nude mice. Fung et al. proposed that PDSS2 is a novel tumor suppressor gene that plays an important role in the development of malignant melanoma (Fung et al., 2009).

The sequence of PDSS2 (AF254956) was firstly submitted to National Cancer for Biotechnology Information by the authors in 2000 and was then named as C6orf210 by Human Genome Organization. Then C6orf210 was found to be important in determining the length of the side chain of ubiquinone in mammals and was named as PDSS2 (Saiki et al., 2005).

Non-small cell lung cancer

Note

Non-small cell carcinomas (NSCLC) are divided into non-small cell lung cancer accounts for approximately 85% of all lung cancers. It is divided further into three main categories: adenocarcinoma, squamous cell carcinoma (SCC), and large cell carcinoma histologies. 6q16.3-21 LOH has been found in 78% of SCLCs. PDSS2 gene is located in the frequent LOH region of 6q16.3-21, implying for its potential role as tumor suppressor. Loss of PDSS2 expression is associated with non-small cell lung cancer. Decrease in PDSS2 expression was more severe in poorly and poor-to-moderately differentiated lung cancers, more in higher pathological stage and in patients with lymph node metastasis. The decrease in PDSS2 expression in tumor tissues was not related to sex or histological type of NSCLC, but was related to smoking history (Chen et al., 2013).

The PDSS2 gene has low expression levels in human lung cancer cell lines. The forced PDSS2 overexpression caused massive cell death through apoptotic pathways and significantly inhibited

colony formation in the NCI-H1299 lung cancer cell line. At the same time, repression of PDSS2 expression by siRNA enhanced the growth of a noncancerous lung epithelial cell line MRC-5. There was an inverse correlation between PDSS2 expression and gelsolin expression, which is known to inhibit apoptosis and enhance cell invasion and metastasis. The ability of PDSS2 to repress gelsolin might contribute to its tumor-suppressing activity. However, PDSS2 did not influence the sensitivity of the lung cancer cells to chemotherapeutic drugs. Taken together, PDSS2 has tumor-suppressing activity in human lung cancer cells by enhancing apoptosis and inhibiting tumorigenic capacity (Chen et al., 2014).

Breakpoints

Note

Studies have reported the potential of the PDSS2 gene as a tumor suppressor in gastric cancer, lung cancer, and melanoma. First, the PDSS2 gene is located in the chromosome region of 6q16.3-21, where frequent LOH occurs in lung cancers, implying the loss of PDSS2 expression and function in lung cancers. Second, PDSS2 protein is essential for the enzyme activity of prenyl diphosphate synthase, which is a critical enzyme in CoQ10 biosynthesis. Decreased PDSS2 level can lead to CoQ10 deficiency. CoQ10 is the predominant human form of endogenous ubiquinone, and plays a vital role in the mitochondrial respiratory chain as the carrier of electrons from complexes I and II to complex III. Its reduced form is one of the most potent lipophilic antioxidants in all cell membranes. CoQ10 also participates in pyrimidine nucleoside biosynthesis and may modulate apoptosis and the mitochondrial uncoupling protein.

By depletion of CoQ10, decrease in PDSS2 may contribute toward the initiation and progression of tumor through deregulated mitochondria function and increased intracellular oxidative stress.

Overexpression of PDSS2 induced apoptosis in cancer cells.

The mechanism is not clear. A possible mechanism could be that CoQs including CoQ10 can selectively inhibit DNA topoisomerase II (topo-II) activity and eukaryotic DNA polymerase-γ, which is a mitochondrial DNA polymerase, and thus inhibit DNA synthesis and mitochondrial proliferation and consequently induce cancer cell death.

An inverse correlation of PDSS2 expression and gelsolin expression was reported. Gelsolin has been shown to inhibit apoptosis by blocking mitochondrial membrane potential loss and cytochrome c release, thus stabilizing mitochondria. Repression of gelsolin by PDSS2 may counteract the mitochondrial stabilization, and thus induce apoptosis in cancer cells.

PDSS2 does not influence the chemosensitivity of lung cancer cells.

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